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## Procalcitonin and cellulitis: correlation of procalcitonin blood levels with measurements of severity and outcome in patients with limb cellulitis

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### ABSTRACT

**Background:** Procalcitonin levels may be raised in bacterial infections and have been used to guide antibiotic therapy. There is little data on procalcitonin and limb cellulitis.

**Objectives:** Within a clinical trial of antibiotic therapy, we examined the correlation between clinical observations, blood tests and local measurements of skin damage, with serum procalcitonin levels.

**Methods:** The data is from a subset of the patients recruited into a clinical trial of antibiotic therapy for cellulitis (clindamycin for cellulitis, NCT01876628) whose procalcitonin levels were correlated with clinical and laboratory measurements. We selected the variables strongly correlated with procalcitonin and evaluated the predictive value of the baseline procalcitonin on the primary trial outcome.

**Results:** 136 patients provided 307 procalcitonin levels which were correlated with 8 variables. The strongest correlations (correlation coefficient of >0.5) with procalcitonin were the affected skin area (0.537), C-reactive protein (0.574) and neutrophil:lymphocyte ratio (0.567). Receiver operator characteristic curves demonstrated poor sensitivity and specificity of procalcitonin in predicting primary outcome. Procalcitonin baseline levels were low but decreased as patients recovered.

**Conclusions:** Procalcitonin levels are generally low in limb cellulitis and cannot be used to confirm the diagnosis or the need for antibiotic therapy. Procalcitonin is a poor predictor of early improvement.

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### KEYWORDS

Cellulitis; limb; procalcitonin; antibiotic; trial; CRP; ROC; renal

### Introduction

Procalcitonin is a biochemical marker which is raised in bacterial infections. It is produced in thyroidal C-cells and other neuroendocrine cells but is also produced by a wide range of cells of extrathyroidal origin in response to bacterial infection (Morgenthaler *et al.* 2003). Procalcitonin blood levels have been used to assist in determining whether a patient will benefit from antibiotic therapy and have been used to withhold antibiotics, as well as to stop antibiotics (Schuetz *et al.* 2009). Cellulitis is a common infection of the skin and procalcitonin has been proposed as a test which could differentiate cellulitis from other inflammatory skin conditions which may mimic cellulitis (Rast *et al.* 2015). Procalcitonin may also have a value in measuring severity of an infection and thus the duration of the patient's symptoms and signs, and as a guide for therapy (Mahmood *et al.* 2016).

Within a clinical trial of cellulitis (Brindle *et al.* 2017), we wanted to examine the relationship between routine blood tests and local measurements of skin damage, from screening and enrolment into the trial, to see if a baseline measurement of procalcitonin might be useful. We also measured levels of procalcitonin on two occasions following antibiotic therapy. All the procalcitonin levels available were assessed for their degree of correlation with other objective variables

measured at the same time. We used the most highly correlated variables to compare their sensitivity and specificity with procalcitonin in achieving primary outcome. We also wished to see whether renal impairment was associated with elevated levels of procalcitonin in the study population.

### Clinical significance

- There is a published data showing low levels of procalcitonin in facial cellulitis.
- There is a retrospective study of cellulitis in which procalcitonin was correlated with severity and which demonstrated low levels in some patients with cellulitis.
- This study is of a prospective group within a clinical trial with sequential sampling for procalcitonin and a pre-defined outcome.
- It shows that levels of procalcitonin are generally low but decrease with recovery. Procalcitonin is not a useful predictor of early improvement.

### Patients and methods

This study used data collected as part of a clinical trial of antibiotic therapy for cellulitis (clindamycin for cellulitis;

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NCT01876628) funded by the UK National Institute for Health Research (PB-PG-0212-27015) and approved by the UK National Research Ethics Service (reference number: 13/SC/0211). The trial compared flucloxacillin with placebo versus flucloxacillin with clindamycin. The trial results showed no significant difference between the two antibiotic regimens in achieving primary outcome; improvement at the Day 5 follow-up visit (Brindle *et al.* 2017).

A subset of the patients sequentially recruited from two centres which were offering routine procalcitonin testing during the latter part of the trial (August 2014 to October 2015), had procalcitonin levels measured at three time points. Patients with cellulitis who were screened for eligibility for the trial during this period but were not enrolled did not provide follow-up samples. Cellulitis was defined using criteria used in the PATCH trial of cellulitis: local warmth, tenderness, or acute pain; unilateral erythema or bilateral erythema, with a temporal association between symptoms and the more severely affected leg; and unilateral oedema. If there was doubt about the certainty of the diagnosis, the patient was excluded (Thomas *et al.* 2013). At screening, or following entry into the trial, blood was drawn at Baseline, Day 5 and Day 10. Procalcitonin was measured using the VIDAS® or Roche Diagnostics B.R.A.H.M.S PCT™ systems.

The primary outcome was improvement at the Day 5 follow-up visit, defined as being afebrile ( $<37.5^{\circ}\text{C}$ ) and having a reduction in limb swelling (measured by limb circumference) or a reduction in erythema (measured by skin-surface temperature) of 0.2 standard deviations or more. The reduction in limb swelling and limb temperature used the difference between affected and unaffected limbs to reduce confounding by ambient temperature, clothing and posture. Only patients with all three values were evaluated for primary outcome in this study.

Medians and geometric (natural logarithm) means have been reported instead of means where the data is skewed. Procalcitonin levels were correlated with clinical and laboratory measurements using the natural logarithm. The size of the correlation coefficient is the degree of correlation between procalcitonin and a variable; the  $p$  value gives the degree of statistical likelihood that this correlation is true. We selected those variables which are most strongly correlated (Pearson correlation coefficient of  $>0.5$ ) with procalcitonin and generated receiver operator characteristic (ROC) curves to evaluate the predictive value of the baseline procalcitonin, and the other variables, on failing to achieve the primary trial outcome. A ROC curve with high sensitivity and high specificity would have a large area under the curve (AUC) and the optimum value would be close to the upper left corner of the chart. Yates corrected Chi-squared test was used for categorical data and a two-sample independent  $t$ -test for equality of means; a  $p$  value of less than 0.05 was regarded as significant. Statistical analysis and ROC curve generation was done using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY).

## Results

One hundred thirty-six patients were included in this study; the baseline characteristics are summarized in Table 1. The

characteristics of this subpopulation are similar to the characteristics of the 410 patients included in the trial. The patients provided 307 procalcitonin values which were correlated with 8 variables, which are summarized in Table 2. Figure 1 summarizes the patient numbers from screening and enrolment to follow-up, with the median procalcitonin values at each point. The geometric mean baseline procalcitonin level, of those with any follow-up levels, was 0.19; reducing to 0.10 at Day 5 and to 0.06  $\mu\text{g/L}$  at Day 10. Of the patients enrolling in the trial, 69 out of 109 (63%) had procalcitonin levels below 0.25  $\mu\text{g/L}$  at baseline. One patient had a level of  $>100$  and was nominated a value of 101  $\mu\text{g/L}$  for the analyses. The strongest correlations with procalcitonin were the total affected skin area, C-reactive protein and neutrophil:lymphocyte ratio.

77 out of the 93 (83%) patients who were evaluable at the Day 5 follow-up achieved primary outcome. This is similar to the whole trial in which 276 out of 328 (84%) evaluable patients achieved primary outcome. Of those patients with procalcitonin levels less than 0.25  $\mu\text{g/L}$ , 52 out of 60 (87%) patients achieved primary outcome compared to 25 of the 33 (76%) patients with PCT levels greater or equal to 0.25  $\mu\text{g/L}$ ; OR 2.08 (95% CI: 0.70–6.19),  $p = 0.297$ .

Receiver operator characteristic (ROC) curves were generated to examine the sensitivity and specificity of procalcitonin levels and the three most highly correlated variables: C-reactive protein, neutrophil:lymphocyte ratio and total affected skin area, against failure to achieve primary outcome. The higher the procalcitonin level the less likely the patient was to have improved at Day 5 (Figure 2 and Table 3). The ROC curve showed that procalcitonin levels had poor sensitivity and poor specificity for predicting outcome. Using a cut-off value of 0.25  $\mu\text{g/L}$  or greater for predicting failure to achieve primary outcome has a sensitivity of 30% and a specificity of 50%.

The geometric mean procalcitonin of the 24 patients with serum creatinine levels of  $\geq 100 \mu\text{mol/L}$  was 0.52  $\mu\text{g/L}$  compared to 0.15  $\mu\text{g/L}$  for the 112 patients with creatinine of  $<100 \mu\text{mol/L}$ ; (log mean difference; 1.24, 95% CI: 2.11–0.37),  $p = 0.007$ . Of the four patients with procalcitonin levels greater than 10  $\mu\text{g/L}$  (actual levels: 10.6, 18.2, 23.3,  $>100 \mu\text{g/L}$ ) the geometric mean creatinine was 184  $\mu\text{mol/L}$  (actual levels: 115, 404, 56, 437  $\mu\text{mol/L}$ ).

## Discussion

This study explores the relationship between procalcitonin and other variables that were measured within a clinical trial of limb cellulitis. Procalcitonin has a reputation of being a valuable biomarker, that has a role in antimicrobial stewardship, and we wanted to examine its role in cellulitis. If the procalcitonin test enabled us to determine that there is an active bacterial infection, then this would strengthen the diagnosis of cellulitis and support the use of an antibiotic. We found that 63% of patients had levels below 0.25  $\mu\text{g/L}$  at baseline, which is generally regarded as a cut-off value above which antibiotic therapy is advised (Schuetz *et al.* 2011). Though the baseline levels of procalcitonin were generally low, they did decrease over time and with recovery. This

**Table 1.** Baseline characteristics of the patients. ( $n = 136$ ).

Mean (SD) age in years	52.5 (18.3)
Male (%)	94 (69)
Leg affected (%)	102 (75)
Temperature ( $^{\circ}\text{C}$ ); Mean (SD)	37.0 (0.6)
Pulse (beats per minute); Mean (SD)	90 (25)
Systolic blood pressure (mmHg); Mean (SD)	118 (25)
Affected skin area as percentage of body surface area; Median and IQR*	5 (5)
Difference in circumference between affected and unaffected limb (cm); Mean (SD)*	2.7 (2.3)
Difference in surface temperature between affected and unaffected limb ( $^{\circ}\text{C}$ ); Mean (SD)*	2.8 (1.6)
Neutrophil ( $\times 10^9/\text{L}$ ); Median (IQR)	6.1 (5.4)
Lymphocyte ( $\times 10^9/\text{L}$ ); Median (IQR)	1.5 (0.8)
Urea (mmol/L); Median (IQR)	4.8 (2.5)
Creatinine ( $\mu\text{mol/L}$ ); Median (IQR)	76 (28)
Albumin (g/L); Median (IQR)	35 (8)
C-reactive protein (mg/L); Median (IQR)	38 (106)
Procalcitonin ( $\mu\text{g/L}$ ); Median (IQR)	0.11 (0.45)

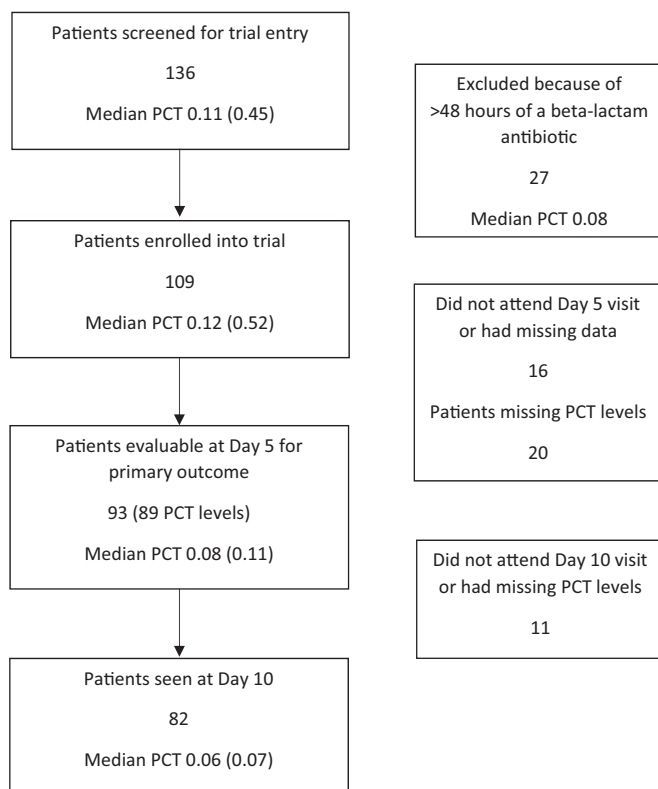
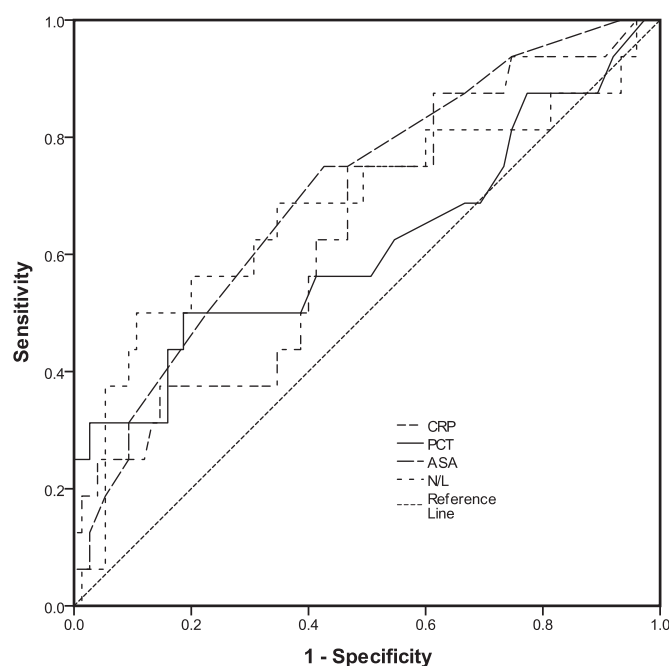
IQR = Interquartile range; SD = Standard deviation.

1% of total body skin area is approximately  $170\text{ cm}^2$ ; 10% of total body skin area is approximately equal to the area of one arm or half the area of a leg.

\* $N = 109$ , as only those patients enrolled had these measurements.

**Table 2.** Correlation between the logarithm of serum procalcitonin and other measurements.

Variable	Pearson correlation	$p$ value
Total affected skin area (% of body surface area)	0.537	<0.001
Difference in circumference between limbs (cm)	0.395	<0.001
Difference in temperature between limbs ( $^{\circ}\text{C}$ )	0.294	<0.001
Neutrophils ( $10^9/\text{L}$ ) (logarithm)	0.456	<0.001
Lymphocytes ( $10^9/\text{L}$ ) (logarithm)	-0.410	<0.001
Creatinine ( $\mu\text{mol/L}$ ) (logarithm)	0.289	<0.001
C-reactive protein (mg/L) (logarithm)	0.574	<0.001
Neutrophil:Lymphocyte ratio (logarithm)	0.567	<0.001
SIRS score at Baseline ( $n = 111$ )	0.267	0.005

**Figure 1.** Flow diagram of patients tested and numbers of test results with median procalcitonin (PCT;  $\mu\text{g/L}$ ) and interquartile range (IQR) values at each point.**Figure 2.** Receiver operator characteristic (ROC) curves for baseline values of procalcitonin (PCT), C-reactive protein (CRP), neutrophil:lymphocyte ratio (N/L) and total affected skin area (ASA) versus primary outcome.

strengthens the hypothesis that cellulitis is a paucibacillary infection with the skin damage being mediated by a variable repertoire of toxins rather than direct bacterial action. It is supported by Bertolus (2016) who did not find procalcitonin to be a useful biomarker for the risk stratification of facial cellulitis, with only 9% of their patients having procalcitonin values above this clinical threshold of  $0.25\text{ }\mu\text{g/L}$ .

There is very limited data on the relationship between procalcitonin and later outcomes. Noh *et al.* (2016) looked at days of hospitalization and showed a significant correlation with procalcitonin and length of hospitalization, but this was also true of C-reactive protein and total white cell count. Given that procalcitonin levels appear proportional to bacterial load one might expect elevated levels in invasive infections and therefore helpful in distinguishing cellulitis from necrotizing fasciitis. Kato *et al.* (2017), in a small series, and

**Table 3.** Areas under the curve (AUC) for the three highly correlated variables and procalcitonin.

Variables	AUC	95% Confidence Interval
CRP	0.64	95% CI: 0.50–0.78
N/L ratio	0.68	95% CI: 0.52–0.84
Total affected area	0.68	95% CI: 0.54–0.81
Procalcitonin	0.63	95% CI: 0.47–0.79

Na *et al.* (2017), in a larger series, found procalcitonin levels to be significantly higher in the patients with necrotising fasciitis than in the patients with cellulitis. A limitation of this study is that we used the primary outcome used for the C4C trial as the outcome to test the predictive value of procalcitonin. This was done to retain compatibility with the trial.

The levels of procalcitonin correlated well with other measures of severity; the amount of affected skin and C-reactive protein and this has been previously reported (Noh *et al.* 2016). We found the neutrophil:lymphocyte ratio to be strongly correlated with procalcitonin and better correlated than neutrophil or lymphocyte counts individually. The potential elevation of procalcitonin levels in renal impairment is recognized and may compromise the value of this test in cellulitis when transient renal impairment is present (Meisner *et al.* 2001). The ROC curve demonstrates the poor sensitivity and specificity of procalcitonin in predicting lack of improvement at Day 5, with no procalcitonin level providing a useful measure of early outcome.

## Conclusion

There does not appear to be any extra information from a procalcitonin test that other routine tests such as C-reactive protein, neutrophil and lymphocyte counts, and local measurements of skin damage already provided.

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## Disclosure statement

No potential conflict of interest was reported by the authors.

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## Data availability

The datasets supporting the conclusions of this article are available in the Dryad Digital Repository, <https://datadryad.org/resource/doi:10.5061/dryad.5q1j0>. The full trial protocol is available from the corresponding author.

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